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Quick guide

IP_3 receptors

Alan Dawson

What are they? Members of a family of intracellular ligand-gated ion channels that allow Ca^{2+} release from intracellular stores. The endoplasmic reticulum (ER), or specialised regions of it, contains ATP-driven Ca^{2+} pumps which generate a high Ca^{2+} concentration in the ER lumen. When inositol 1,4,5-trisphosphate (IP_3) binds to IP_3 receptors, the channel region of the receptor opens, allowing Ca^{2+} to flood out into the cytosol.

How and when did they become famous? In 1983, Hans Streb, Robin Irvine, Mike Berridge and Irene Schulz showed that IP_3 released Ca^{2+} from stores in permeabilised cells. A variety of cell types were found to have high-affinity IP_3 binding sites on their intracellular membranes. The high-affinity IP_3 binding protein was found to be identical with a high-abundance protein, P400, previously found in the cerebellum and to be a cation channel which was opened in the presence of IP_3.

What do they look like? The receptor has four subunits, each of around 2700 amino acid residues. The carboxy-terminal region of each subunit probably has six transmembrane segments, and these interact to form the channel region. Each subunit has a large cytoplasmic domain containing a variety of regulatory sites. The IP_3 binding site is close to the amino terminus, and there is a long regulatory region between there and the channel. Very little of the protein projects into the lumen of the ER. In mammals and birds, there are three IP_3 receptor subunit isoforms, types 1, 2 and 3, plus some splice variants. Type 1 is present at a high level in neuronal tissue, particularly Purkinje cells. Receptors can occur as either homotetramers or heterotetramers.

Any living relatives? Its overall structure and some of its properties are similar to those of the ryanodine receptor, another ligand-gated Ca^{2+}-release channel. Ryanodine receptors are gated by Ca^{2+} and some isoforms are sensitised by cyclic ADP ribose; they are the main routes for Ca^{2+} release in muscle cells, but are also present in other cell types. Various other intracellular Ca^{2+}-release channels have been identified, for example those gated by NAADP. In many cases, IP_3 receptors and ryanodine receptors act together to generate Ca^{2+} signals.

So IP_3 is the signal for Ca^{2+} release... Not quite as simple as that! IP_3 receptors are also potently activated by Ca^{2+} on the cytosolic side, so like ryanodine receptors they also show Ca^{2+}-stimulated Ca^{2+} release — but only in the presence of IP_3. IP_3 and Ca^{2+} act as co-agonists to cause Ca^{2+} release. There is an essential glutamate residue, close to the channel region, which is required for Ca^{2+} stimulation. Ca^{2+} at higher concentrations inhibits IP_3 receptors, so they show a bell-shaped dependence on cytosolic [Ca^{2+}] (Figure 1). The complex interplay between positive and negative feedback from Ca^{2+} that has just been released from the channel is responsible for the generation of local Ca^{2+} signals

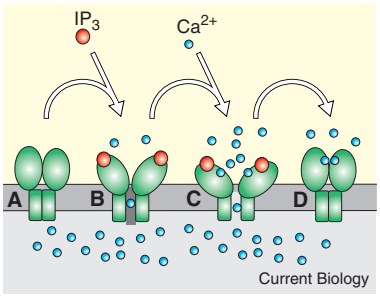

Figure 1. Possible behaviour of the IP_3 receptor tetramer (only two of the four subunits are shown). The unliganded receptor (A) can bind IP_3 to form an open channel (B), with a low open probability (grey). Ca^{2+} released through the channel can bind to cytosolic Ca^{2+}-binding sites to form a new open state with a much higher open probability (C). This is Ca^{2+}-stimulated Ca^{2+} release, leading to spread of the Ca^{2+} signal. As cytosolic Ca^{2+} near the mouth of the channel reaches very high levels, the receptor can flip into a Ca^{2+}-bound inactive state (D).

and for conversion of local signals into intracellular and intercellular Ca^{2+} waves. ATP greatly increases the open-probability of IP_3 receptors in the presence of IP_3 and Ca^{2+}.

Known associates... IP_3 receptors have a very well-documented — but poorly understood — interaction with calmodulin. In general, Ca^{2+}–calmodulin inhibits Ca^{2+} release, but this is not necessarily the same Ca^{2+} inhibition as the one we have just been talking about. A lot of other proteins have also been found lurking suspiciously in the neighbourhood: FKBP12 and calcineurin (phosphoprotein phosphatase 2B) are two suspects. The neuronal Ca^{2+}-binding protein CaBP1 has been shown to activate IP_3 receptor channels, even in the absence of IP_3. In secretory granules of neuroendocrine cells, luminal chromogranin A increases channel activation by IP_3, and in the nematode *Caenorhabditis elegans*, an interaction has been demonstrated between myosin II and IP_3 receptors. Particularly significant is a possible association with members of the Trp family of plasma membrane Ca^{2+} channels that might control Ca^{2+} entry into cells.

Other endearing properties... Very complex kinetic behaviour, which causes successive packets of Ca^{2+} to be released in response to small increments of IP_3 concentration — so-called quantal Ca^{2+} release — has provided years of fun for a brave band of Ca^{2+} kineticists.

Where can I find out more?

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Biological Sciences, University of East Anglia, Norwich NR4 7TJ, UK.
E-mail: A.Dawson@uea.ac.uk